REMARKS

Claims 32-72 were examined and rejected under various grounds as discussed below.

Claim 32 is further amended as discussed below.

Applicants thank the Examiner for withdrawal of the rejection of claims 39-48 and 53 under 35 U.S.C. § 112, second paragraph in response to Applicant's amendment.

No new matter is being introduced, and entry of these amendments and the remarks below are respectfully requested.

I. REJECTION UNDER 35 U.S.C. § 102(b) (Lack of Novelty)

Claims 32-33, 35-41, 44-52, 54-56 and 58-60 remained rejected as anticipated by Hogan *et al.* (U.S. Pat. 5424413, Jun. 13, 1995). (hereinafter, **"Hogan"**). Applicant notes that claims 34, 42, 43, 53, 57, and 51-72 are free of this rejection.

The Office characterized Hogan as disclosing a nucleic acid hybridization probe and method of use. Applicants have listed all the reasons the Office applied in its analysis in their last response and will not repeat that here. Based on the same analysis the teachings of **Hogan** were said to anticipate the limitations of the claims.

Office's Response to Applicant's Prior Amendment and Remarks

Applicants newly added "wherein" clause in claim 32 was interpreted as being directed to "intended use" only. The instant claims are drawn to a pair of oligonucleotide probes with the elements as recited in the claims. **The target nucleic acid D is not a part of the probe,** but is intended to be used along with the probe. Intended use does not have patentable weight in product claims. Because **Hogan** allegedly discloses each element of the claimed probes, the rejection was maintained.

Applicant's Response

The Office contended that the newly added features in Applicant's last amendment, *i.e.*, hybridizing T1 and T2 with S1 and S2, respectively and ligating the 3'-end of T1 with the 5'-end of T2, was merely a recitation of "intended use."

Indeed the target nucleic acid is not part of the probe, but the target nucleic acid is essential in the design of the probes - both of **Hogan** and the presently claimed probes, as explained below. It is instructive to analogize to a 'socket-and-plug' type arrangement: the design of one of these elements (the plug) must take into consideration the "design " of the elements with which it is supposed to interact (the socket).

Amended Claim 32 no longer refers to the intended use, but rather to the positions of the probe segments in the probe nucleic acid molecule; these segments are defined by the target sequence for which they were designed.

When comparing the positioning of the elements of the **Hogan** probe design, *i.e.* two separate nucleic acids, with the design of the presently claimed two probes, a clear difference is evident. As illustrated schematically in the attached Figure 1A (submitted herewith as Appendix) shows the designed of the present probe (left panel) and the probe according to **Hogan** (right panel), taking a target sequence as a starting point. Probe 1 (P1) is defined by having the clamp segment at its 5'-end, and Probe 2 (P2) by having the clamp segment at its 3'-end. The target sequences for which Probe 1 or Probe 2 are designed are designated, respectively, S1 and S2.

Comparing the sequences of the present probes with those of **Hogan** (shown in Fig 1B) emphasizes the difference in the sequences. Although the clamp segments are at the same position within each probe (underscored in Fig. 1B), the ***target specific*** segments are different. The target specific section at the 3'-end of present P1 is found at the 5'-end of **Hogan's** P2, and the target specific region at the 5'-end of present P2 is found at the 3'-end of **Hogan's** P1

Furthermore, in the target sequence of the present claims, the 5' end of S1, is located adjacent to the 3'-end of S2. In contrast, in the **Hogan** design, this is reversed so that the 5'-end of S1 cannot be adjacent to the 3'-end of S2 (Fig. 1A). The difference in design between the present invention and that disclosed by **Hogan** can only be expressed in the claims by including in the claim the position of S1 and S2 relative to each other, because it is only in relation to the target sequence against which probes were designed that this design difference becomes apparent.

Thus, claim 32 has been amended to refer to the target sequence "wherein S1 and S2 are located essentially adjacent to one another in D, and wherein the 5'-end of S1 is adjacent to the 3'-end of S2".

This amended language is not based on, or related to, "intended use." Rather it includes essential features designed into the probes. The probe design of the present claim clearly falls outside of the scope of the **Hogan** design. None of the figures in **Hogan** describes a situation in which the 5'-end of S1 is adjacent to the 3'-end of S2 in the target sequence. Likewise, **Hogan** neither describes any other configuration of hybridized probe and target nor does **Hogan** allow for the possibility of any other configuration (of hybridized probe and target).

Hence, claim 32 now describes the structural attributes of the two probes, which are clearly distinct from the structural attributes of the two nucleic acids of the probe disclosed by **Hogan**.

For the foregoing reasons, it would be proper to withdraw this ground for rejection under § 102.

II. REJECTIONS UNDER 35 U.S.C. § 103 (Obviousness)

Claims 34, 42-43, 57, 61-72 remained rejected as being obvious over **Hogan** as applied and discussed above, in view of Zhang *et al.* (5,876,924, issued 03/02/1999). (hereinafter, **"Zhang"**).

Admittedly, **Hogan** did not disclose

- a junction site between S1 and S2 as recited in claim 57, or
- the method step (c) and (d) for detection of a target nucleic acid in a sample as recited in claims 61-63, and 67.

Zhang was cited for its alleged disclosure of "an improved method" which enables rapid, sensitive and standardized detection and quantitation of nucleic acids from pathogenic samples from a patient (col. 3, lines 11-15). The method allegedly applies a pair of non-overlapping oligonucleotide amplification probes (col. 3, lines 62-66) which Zhang calls "capture/amplification" probes and an amplification probe (see col. 3, lines 66-67). These are said to be complementary to adjacent regions of a target (col. 4, lines 3-8) and do not overlap (col. 4, lines 8-9). The two probes are joined by a ligating agent (col. 4, lines 9-11). In the method, the ligated amplification sequence is directly detected (col. 4, lines 16-19), and the two amplification probes may be ligated to form contiguous sequence that is then amplified (col. 4, lines 24-26). The PCR products are subject to electrophoresis for detection (see column 16, lines 25-35).

According to the Office, a skilled artisan would have been *motivated* to construct a probe comprising the terminal segments of the **Zhang** probe which can be ligated after the terminal segments are hybridized to a target nucleic acid at an adjacent position. One of ordinary skill in the art allegedly would have also been motivated to apply an amplification method for detecting a target nucleic acid taught by **Zhang**. because the method of **Zhang** is "an improved method" which allows rapid sensitive detection and can be performed in microtubes or microplate wells (see column 3, lines 19-27). It would have therefore been *prima facie* obvious to perform the steps as recited in claims 61-69.

The Action admits that **Hogan** does *not* disclose the limitations of claims 42 and 43 that GC content (in the arm region) is >80% or between 90% and 100%, respectively. However, attention is focused on the disclosure that the **Zhang** capture/amplification probe has a GC

content at least 60%, so that it exhibits minimal secondary structure (hairpin, fold back). This led the Office to conclude that a skilled artisan would have been *motivated* to design an oligo probe comprising a GC content >80% or between 90% and 100% as allegedly taught by **Zhang**. The motivating factor is supposedly the notion that the probes would exhibit minimal secondary structure. So, the Office's conclusion was that it would have been *prima facie* obvious to design an oligo probe with GC content >80% or between 90% and 100% (*i.e.*, as claimed in claims 42 and 43).

The Action further admits that **Hogan** does not disclose a kit comprising probes and reagents for detecting target DNA in a sample (present claims 70-72). However, this is allegedly provided by **Zhang** which discloses a kit comprising probes and reagents for detection of an amplified ligated DNA sequences (col. 25, lines 7-36). The Office alleges that the skilled artisan would have been *motivated* to construct such a kit (as taught by **Zhang**) for convenience because this as a routine practice in the art. This is the reason that the kit claims (71-72) were considered to be *prima facie* obvious.

Office's Response to Applicant's Prior Amendment and Remarks

Applicant argued that **Zhang** does not disclose that the capture/amplification probes contain any a GC rich region that could serve as a "clamp", and that **Zhang** only disclosed one end of the probe to be GC rich. However, according to the Office, **Zhang** disclosed the benefit of using GC rich regions (see column 36, lines 1-3), so that one of ordinary skill in the art would have been motivated to design an oligonucleotide probe with a GC content >80%, or between 90% and 100%, in clamp regions.

Applicant's Response

Applicants do not dispute that **Zhang** discloses a design in which terminal segments of two different probes that hybridize to a target can be ligated and may thereby increase the specificity over a single probe design (**Zhang**, Figs. 4 and 6).

Hogan teaches design of a nucleic acid probe that comprises two nucleic acid molecules, and has two separate target regions each of which hybridizes to a target nucleic acid. The **Hogan** probes comprise two distinct arm regions that may also hybridize with one another, but will not do so in the absence of a target nucleic acid. Only in the presence of a target nucleic acid will complementary arm regions of the **Hogan** probe (comprising the two nucleic acid molecules) hybridize to one another, forming a branched nucleic acid structure (See **Hogan** abstract and **Hogan** Fig. 2A.)

Thus, **Hogan** conveys to one of ordinary skill in the art a probe design comprising two nucleic acids that form a branched nucleic acid when hybridized to a target sequence. However, the skilled artisan will immediately appreciate that the two nucleic acids of the **Hogan** probe cannot be ligated to each other. Even if such a person tried to combine the **Hogan** probe design with the concept of ligating probes according to **Zhang**, he/she would arrive at designs that differ clearly from the current invention. This is depicted in Figure 2 of the attached Appendix and is explained below.

Option 1: Combining **Hogan** (a probe which comprises two nucleic acids) with **Zhang** would lead one to design two probes, each comprising two nucleic acids, which may hybridize adjacent to each other such that the nucleic acid of the first probe may be ligated to the nucleic acid of the second probe. (See Fig. 2, Option1.)

Option 2: Alternatively, **Hogan** also teaches a branched probe based on three nucleic acids (see Figures 3A/B of **Hogan**). Combining that with **Zhang** would lead one to a design in which a first probe comprising two nucleic acids may hybridize adjacent to a second probe such that a nucleic acid of the first probe may be ligated to the second probe. (See Fig. 2, Option 2.)

Option 3: Importantly, the skilled artisan seeking to use a branched design and wishing to use only two probes/nucleic acids as taught by **Zhang** would not be led to the present invention, because he would arrive at a probe design in which the two probes cannot be ligated (See Fig. 2, Option 3.)

So when the **Zhang** and **Hogan** disclosures are combined, there is no suggestion of the present probe design. Rather, what is suggested is a design such as Option 1 and Option 2 (of Appendix Fig. 2). Inventive-conceptive skill would be needed to attain a completely new probe design, as presently claimed, that is **not** the typical branched nucleic acid of **Hogan** (Appendix Fig. 1)

The following additional important point bears consideration. According to the **Zhang** method, a capture step, is essential and, therefore, always included in the method. See steps (a) and (b) of **Zhang** claim 1. This capture step takes place prior to ligation step (c). No such capture step is required for the claimed probes and their use. Thus, the skilled artisan would not have been led to the present claims when combining **Zhang** with **Hogan**, because, he would not arrive at the probe design needed for practice of the present method (see, Claim 61, step (a)) let alone a method that excludes a capture step.

Accordingly, the claimed method (claim 61 and the claims dependent therefrom), is non-obvious as is the probe design used in step (a) that too is novel and non-obvious (as discussed above). Again, the claimed method does not comprise a capture step as taught by **Zhang**.

Thus, for the reasons advanced above, the Office is urged to withdraw the rejection under § 103(a) of claims 42-43, 57, 61-72.

III. CONCLUSION

Applicants respectfully request entry of the foregoing claims and Remarks, and reconsideration of the rejections and allowance of the present claims.

Respectfully submitted,

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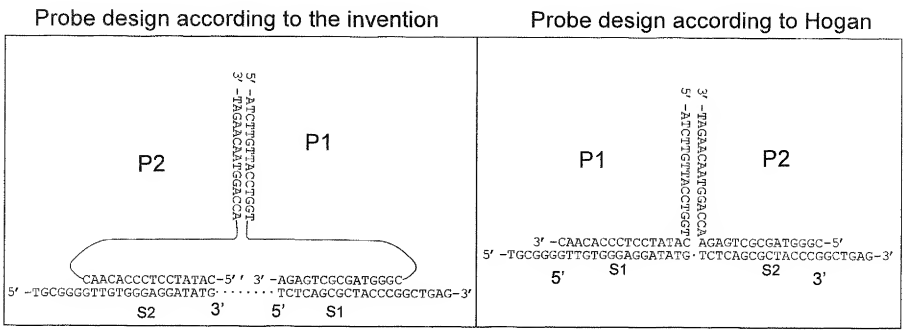
Figure 1

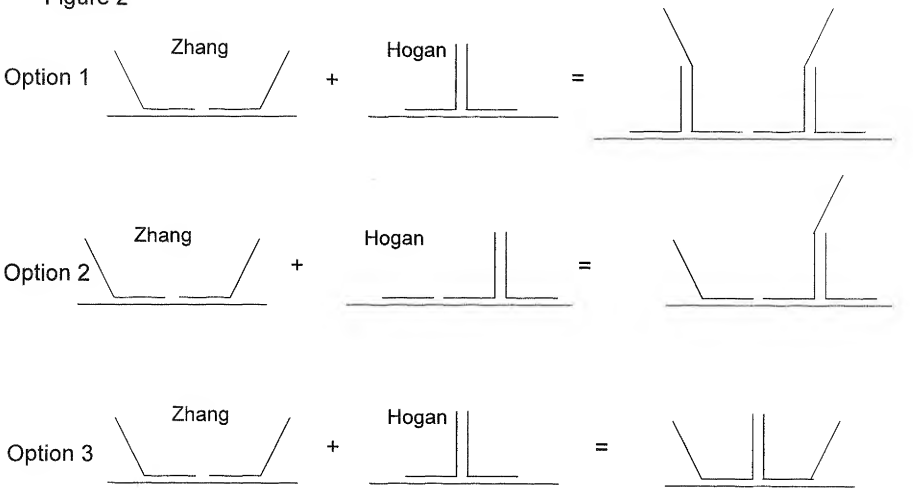
A



B

P1 according to the invention	5′ -ATCTTGTTACCTGGT---CGGGTAGCGCTGAGA-3′
P2 according to the invention	5′ -CATATCCTCCCACAAC---ACCAGGTAACAAGAT-3′
P1 according to Hogan	5′ -ATCTTGTTACCTGGT···CATATCCTCCCACAAC-3′
P2 according to Hogan	5′ -CGGGTAGCGCTGAGA···ACCAGGTAACAAGAT-3′

Figure 2


Option 1
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